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EXAMINER
WESSENDORF, TERESA D

ART UNIT	PAPER NUMBER
1639	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/852,910	Applicant(s) GILCHRIST ET AL.	
	Examiner T. D. Wessendorf	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-101* is/are pending in the application.

4a) Of the above claim(s) *2,10-12,20,25-32 and 34-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,13-19,21-24 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-30, 33 and 34 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that group II should be examined with group I. There is no additional search to examine these groups. Upon careful reconsideration of the restriction requirement, the restriction is revised. Group II, as applicants stated, is identical to the steps of claim 29 of Group I. Therefore, groups I and II are rejoined.

Applicants argue that the claims of groups III, IV and XIV be rejoined with each other. It is argued that group III is classified in the same class/subclass. A search and examination of these two claims will not result in any additional burden to the examiner. In response, the search is not limited only to U.S. Patents class/subclass classification. Rather, the literature and foreign patents are extensively searched for the distinct inventions. The U.S. Patents search is not co-extensive with the foreign and/or literature searches.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of the species 1, testing for binding to at least an intracellular fragment of GPCR; 2, Ai subunit of

fragment based on peptide length from 7-70 amino acids; 3. method of signaling activity is measuring ligand binding; 5, LQLNLKKYNRV, SEQ. ID. 243 in Paper No. 11 is acknowledged. Note that the peptide length of 11 amino acids will be examined as based on Seq. ID. 243.

Claims 2, 10-12, 20, 25-32, 34-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11. [Note that the claims to ELISA have been withdrawn. ElISA is drawn to a protein-peptide fusion display library, which is not the elected peptide library species that is non-fused.]

Status of Claims

Claims 1-101 are pending in the application.

Claims 1, 3-9, 13-19, 21-24 and 33 are under examination.

Claims 2, 10-12, 20, 25-32, 34-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and specie, as stated above.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this

application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations in the residence made to the oath or declaration by inventor Gilchrist.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 35, paragraph [0069]. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors {typographical e.g., undercamer at page 49, [0100], grammatical and/or idiomatic}. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear,

concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-11, 13-19, 21-24, 28 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method utilizing a biased library derived from the carboxyl terminus of the Gα-coupled receptor as the peptide library and specific peptide library for the candidate compounds does not reasonably provide enablement for a method using any or all types of G-protein coupled receptor (GPCR) for the peptide library or candidate compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the claimed invention is drawn to an infinite or undefined number of variables. The scope of the claim is not commensurate in scope with the enabling disclosure. The specification at e.g., page 49 of the Examples discloses a method to identify an inhibitor using a known biased peptide library from the carboxyl-end of the GPCR. It is not apparent from the examples as to its applicability to the wide range of biologically active receptors such as hormone, viral and other GPCR in general. The showing in the examples is limited to specific peptide library, candidate compounds and receptors for

the GPCR. Other than the specifically exemplified components of the methods, the disclosure simply provides general statements. One skilled in the art would have not deemed the specific examples of a known binding ligand to a known receptor to be predictive to an unknown or unidentified receptor(s) of any GPCR-binding ligand obtain from a library of an infinite combinations of peptide and/or non-peptide compounds. In a highly unexplored and very unpredictable art as GPCR reactions, one cannot make a priori statement. This is evident from the results in the Examples. It shows the effect of some of the specific analogs from no effect of binding to the receptor to a significant binding effect. See the disclosure at page 16, paragraph [0046] that discloses that the interaction between a G protein and a GPCR is quite specific. For example, a difference in one amino acid can substantially reduce or eliminate the ability of a G protein peptide to bind to its receptor. See also Osawa et al (The Journal of Biological Chemistry) at page 31052, the abstract. If applicants have already encountered the unforeseen or unpredictable effects, how much more for one skilled in the art given the limited direction or guidance in the specification? It would take undue amount of experimentation for one skilled in the art to practice the claimed invention. The factors to be considered in a determination of undue

experimentation are disclosed in *In re Wands,* (U.S.P.Q. 2d 1400 (CAFC 1988). These factors are as follows: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability of the art and the breadth of the claims.

1). The specification fails to give adequate direction and guidance in how to readily go about determining which are the G-proteins that can be made into a library. The numerous, different receptors to which the numerous, different G-proteins can bind to. The residues that can be modified to form a library and the candidate compounds that forms the candidate library

2). The specification failed to provide working examples for any type of G-proteins, its receptors, the method of making the different libraries and an expression vehicle that can accept a G-protein ligand without deleterious effects to the vehicle (vectors and/or hosts) being used.

3). The breadth of the claims encompasses a large diversity of expression vectors, nucleic acids encoding peptides, peptide combinatorial libraries, candidate compound library, G-protein ligand binding receptor and receptors. It is well known in the art, that it is often difficult to know what the expression level of specific peptides or peptide fusions is; in many cases,

even an average measure of expression level is difficult to obtain. The diversity of the inserts is not easily estimated. It may be for example, that only a small subset of possible peptide sequences are presented efficiently by a particular expression system. And, it is not always easy to follow the expression of peptides in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert.

4). The state of the prior art is such that while techniques or the expression of determinants on the surface exist only for the well studied vectors as phages, receptor and its ligand, however, even with phages, limitations are known to exist. For example, there are phage vectors that could cause protein domains that contain disulfide bonds in their folded forms not to fold.

5). The art is inherently unpredictable because even one surface peptide is identified in a candidate genetic package it is not possible to predict what effect the insertion of a foreign sequence into the protein will have on the protein or the genetic package *a priori*. Likewise, it is not possible to predict which variations of amino acids or combinations of amino acids would result in the proper expression of the protein and therefore proper contact with the target molecule. It is generally known that the conformational freedom that promotes

binding, e.g., by modifying the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the fusion in ways difficult to predict and measure.

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous undefined variables would display an inhibitory peptide that inhibits a binding ligand to a receptor domain without undue experimentation. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-11, 13-19, 21-24, 28 and 33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step of "providing" for the library based on the native binding peptide. Likewise, the step of screening such that a high affinity binding is obtained and/or the selection step. "High" is a relative term which renders the claim indefinite. It is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. "The native peptide" lacks antecedent support from the preceding statement. There is no nexus between the preamble and the body of the claim or at least they are at odds with each other. The preamble recites for identifying an inhibitor while the body of the claim recites for a candidate compound.

B). Claim 3 is indefinite as to the metes and bounds other 'at least an intracellular fragment' of the GPCR. It is not clear as to the testing step such that binding is achieved, especially for an infinite intracellular fragment of the receptor. It is not clear as to the number of intracellular fragment of a GPCR.

C). Claim 13 is indefinite as to the step of the "at least two sequential binding assays" of the components. The metes and bounds of the numbers of sequential binding assays is not clearly set forth.

D). Claims 14-17 are indefinite as to step of the competitive binding assay or the components involved therein.

E). Claims 18-19 broaden the base claim. The base claim does not recite for a detectable signal for each and every members of the library. "Capable" connotes uncertainty as to whether a signal is definitely detected.

F). Claims 21-23 are unclear as to its reference of "activating ligand' in the step of signal generation and/or determination.

G). Claim 28 is indefinite as to the metes and bounds of a "focused library", especially in the absence of positive definition in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the

art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 13-19, 21-24 and 33 are rejected under 35 U.S.C. 103(a) as being obvious over Coughlin et al (U.S. 5,892,014) or Fowlkes et al (WO 98/19162) in view of Gilchrist (The Journal of Biological Chemistry).

Coughlin et al discloses at col. 2, line 50 up to col. 4, line 50 a method for identifying compounds that specifically interact with and modulate the activity of a cellular receptor. The method includes screening polypeptides in a library to identifying those polypeptides which agonize or antagonize receptor bioactivity. The method uses a library of recombinant cells, each cell includes (i) a target receptor protein whose signal transduction activity can be modulated by interaction with an extracellular signal, the transduction activity being able to generate a detectable signal, and (ii) an expressible recombinant gene encoding an exogenous test polypeptide from a polypeptide library. By the use of a variegated gene library, the mixture of cells collectively express a variegated population of test polypeptides. The polypeptide library can be generated as a semi-random peptide library (e.g., based on combinatorial mutagenesis of a known ligand). Coughlin discloses that the (assay) method may be modified by the introduction of a

step in which the recombinant cell is first contacted with a known activator of the target receptor to induce the signal transduction pathways from the receptor. In one embodiment, the test polypeptide is assayed for its ability to antagonize, e.g., inhibit or block the activity of the activator. Alternatively, the assay can score for peptides from the peptide library which potentiate the induction response generated by treatment of the cell with a known activator. As used herein, an "agonist" refers to agents which either induce activation of receptor signaling pathways, e.g., such as by mimicking a ligand for the receptor, as well as agents which potentiate the sensitivity of the receptor to a ligand.

Fowlkes basically discloses the same method as Coughlin. See e.g., page 128 and the claims. Each of the Coughlin or Fowlkes references does not expressly recites that the library of peptide is based on G-protein. However, Gilchrist discloses at page 14914, col. 2 up to page 14918, a method by which a library from the carboxyl terminus of the Gα subunit of the G-protein is made into a combinatorial library, screened for its binding effect with adenosine receptors (rhodopsin receptor is cited in the abstract). The peptides obtained from the screening are then tested in an agonist-antagonist competition. See specifically the Experimental Procedures at page 14913 up to

page 14914 for a detail description of the method. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use a G-protein based on its native sequence in the method of Coughlin or Fowlkes, to test its binding effect for its receptor, as taught by Gilchrist. (Coughlin teaches or at least suggests the method as applied for said GPCR.) One having ordinary skill in the art would have been motivated to use the G-protein peptide as taught by Gilchrist since it is known in the art to as this is where binding resides for the receptor. The use of the method of Coughlin using a library for a compound as the G-protein will lead to the discovery of pharmaceutically effective compounds as disclosed by Coughlin or Fowlkes.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
April 16, 2003